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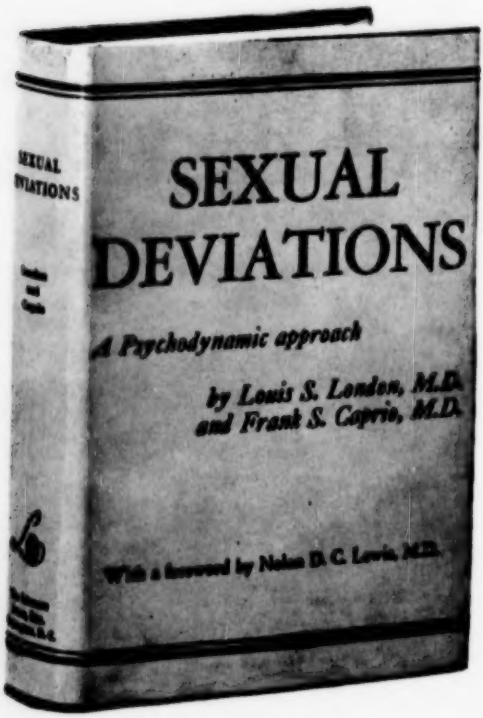
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Hereditary Aspects of Arteriosclerosis*

MURRAY ISRAEL, M.D.

Director, Vascular Research Foundation, Roslyn, N. Y.

When Dr. Koerner asked me to discuss the hereditary aspects of arteriosclerosis before your group, it seemed a simple problem. However, to concentrate on one phase of a subject as complex as arteriosclerosis without showing a complete picture of the disease might result in a not too profitable evening. In the time allotted to me, then, I shall attempt first to review the whole problem broadly, simply, clearly and rapidly: secondly, to concentrate on the hereditary aspects, and then instead of delving into a discussion of dominant and recessive genes, homozygotes and heterozygotes, etc., to explore the manner in which an investigation of this hereditary disease can contribute to the future control of arteriosclerosis.

I am indebted to Dr. Frank Netter, international authority on simplifying complex medical problems artistically, for this slide, a beautiful, schematic presentation of all causative or etiologic factors, which should make even more clear a subject I am anxious to keep simple. Keeping this visual image foremost in your mind throughout this talk will perhaps make it easier to understand the subject matter when it would appear that I might be going off on a tangent.

It is at this time that the difference between a chronic disease of metabolism such as "hardening of the arteries" and a disease such as pneumonia might best be pointed out. An analogy might be drawn in the spheres of music and of medicine. A monophasic disease such as pneumonia, caused by an infectious agent and specifically cured by an antibiotic drug, is comparable to a solo. When we consider a symphony, with its many instruments and arrangements, the conductor and the numerous orchestra members, the acoustics, etc., and compare this complex, integrated polyphonic expression with the solo, it is clear that although both solo and symphony are music, the difference between the two is tremendous.

Similarly, when we consider "hardening of the arteries" and the multiple causative or etiologic factors involved in this terrible scourge of mankind—dietary, traumatic, hormonal, infectious, chemical and last but possibly the most important, hereditary—the immeasurable difference between arteriosclerosis and pneumonia is obvious, although both come under the heading "disease." Prior to defining atherosclerosis, I should like to discuss the end results of this disease.

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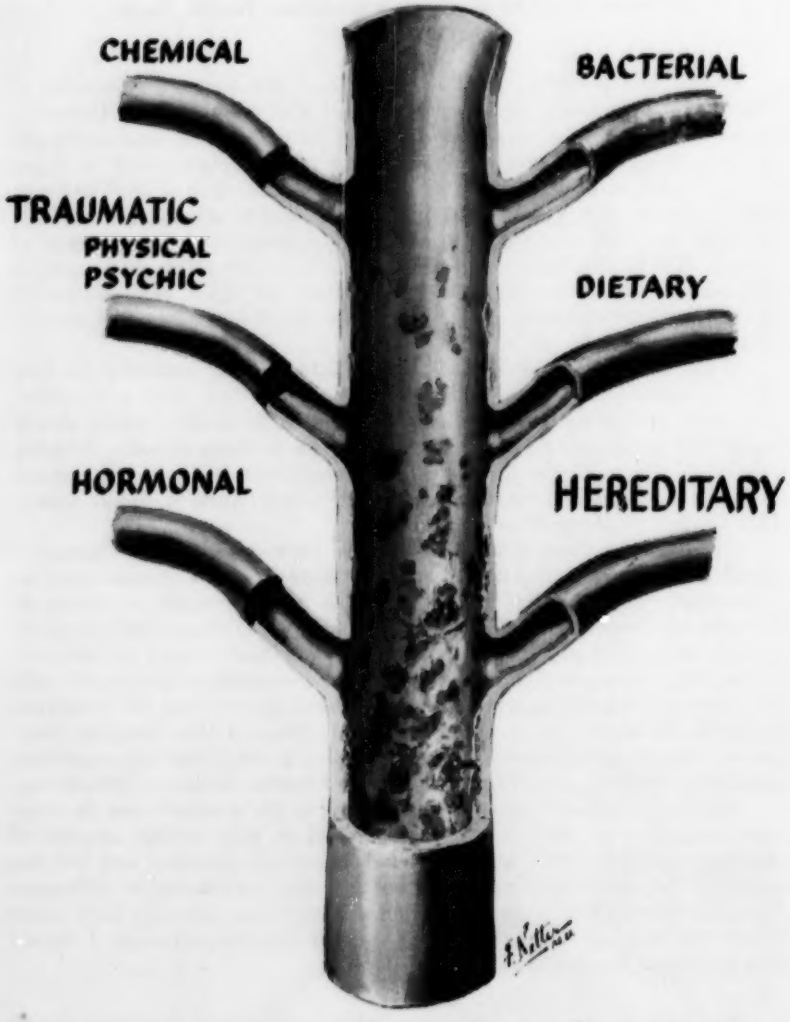
*Read before the Division for Education in Heredity and Eugenics of the National Research Foundation for Fertility, Inc., January 20, 1950.

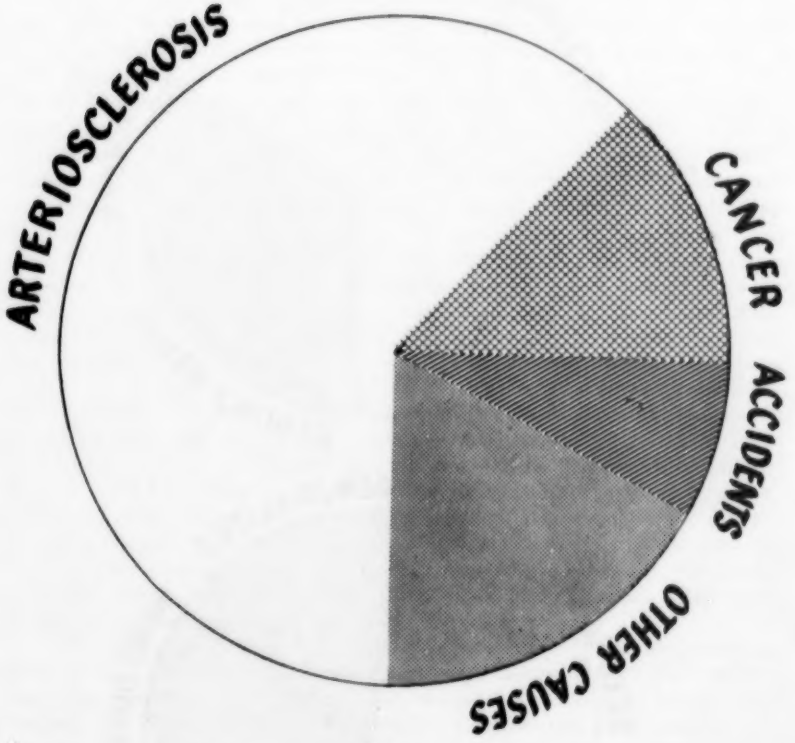
ETIOLOGICAL FACTORS



SLIDE 1

MORTALITY STATISTICS

General Population



SLIDE 2

In Slide 2 we are given general mortality statistics and it is evident that arteriosclerosis is the most fatal of all diseases. The average person if asked which diseases have the biggest mortality rate would probably answer, "cancer and poliomyelitis." The public mind has been taught to think of cancer as the most malignant and of poliomyelitis as the most crippling. However, the medical profession knows that arteriosclerosis is, in mortality statistics, the *most killing* and in its thousands upon thousands of victims the *most crippling.*

No actual percentages are given on the slide, as these are subject

MORTALITY STATISTICS

(from Journal of A.M.A.—Sept. 24-Oct. 8, 1949)

SLIDE 3

to continual change. It makes little difference, however, whether the percentages are 60 to 70 or 80; the main purpose is to show the importance of the subject of arteriosclerosis to all of us. Since some of the material used in this lecture is drawn from two issues of the *J. A. M. A.*, September 24, 1949 and October 8, 1949, it seemed propitious to analyze in the obituary columns of these issues the deaths of those whose duty it is to treat this killer. It can be seen from Slide 3 that doctors are afflicted with this disease slightly more than the general population. The lower one-half of this illustration is a diagnostic breakdown of the white segment of the upper one-half labeled "arteriosclerosis." This paradox, the preponderance of arteriosclerosis in the medical profession, should give us pause. It accentuates the problem of arteriosclerosis control: a patient usually feels a sense of hopelessness when the doctor who believes in the senescence theory says, "hardening of the arteries is simply a phenomenon of aging: nothing can be done about it, as no one can escape age and death." He asks the patient to accept it by saying, "all you have to do is be philosophical, adjust to your new limitations, take it easy, retire, don't be nervous, don't do this, don't do that, etc." As a result a Gilbert and Sullivan philosophy—"let the punishment fit the crime"—has evolved to justify any sudden coronary death, to wit: if the patient was old, he died a natural death. If young, his "number was up." If old and good, he lived a full life and nature took its course. If young and good, the good die young. If old and bad, the scoundrel was too miserable to die. If young and bad he "had it coming." If old and recently married, he had probably engaged in an overzealous Freudian pursuit. If wealthy, high living. If poor, he's better off dead. If an athlete, an athletic heart. If a recently jilted lover, a broken heart. If an ordinary mortal like most of us—neither good nor bad, neither young nor old, neither rich nor poor—it was "in the book." Actually, the cause of death was a disturbance of metabolism which eventually led to the occluding of the coronary artery.

This attitude of resignation toward the real killer of mankind must go! The senescence theory, like the disproved conception that the earth is flat, must be eradicated from our thinking. I mention the above tragicomedy not in an attempt to expose to ridicule our great medical profession, since no one is more grateful than I for the tremendous opportunities allowed me to follow the search for truth. I mention it because it is the present attitude which doctors and patients alike seem to accept and which I myself until recently followed. The purpose of Slide 4 is to place atherosclerosis into the proper focus. In this talk our concern is with type No. 5—*intimal lipoidosis or atheromatosis.* Numbers 1 to 4 are types showing early changes in the intima. Numbers 6 to 13 are types which are at present not amenable to specific therapy, although there is reason to believe that a hormone-vitamin approach utilizing adrenal factors will eventually make these types of arteriosclerosis unimportant. Since atheromatosis, however, superimposes itself on the other types, and, by gradually occluding the lumen of an artery, finally applies the coup de

Anatomic Types of Arteriosclerotic Lesions

1. Intimal mucinosis
2. Intimal hyalinosis
3. Intimal fibrosis
4. Intimal elastosis
5. Intimal lipoidosis (atheromatosis)
6. Intimal calcinosis (ossification)
7. Medial mucinosis
8. Medial fibrosis and hyalinosis
9. Medial amyloidosis
10. Medial calcinosis (ossification and cartilage formation)
11. Medial fibrinoid necrosis
12. Medial cystic degeneration
13. Degenerative and necrotizing fibrinoid angiopathy.

SLIDE 4

grace, it offers at present the most important problem. Paradoxically enough, it has recently become the most amenable to treatment. Those who wish to seek the latest approach should read "Prevention and Treatment of Atherosclerosis" in the October 8, 1949 issue of the *J. A. M. A.* Had the title been "Prevention of Dropping Dead" or less brutally "Prevention of Passing Away" you would probably have needed no introduction to it.

We have not discussed the hereditary factors, but we shall do so after a review of the Hueper anoxemia theory of arteriosclerosis. However, before discussing Dr. Hueper's theory, it may not be amiss to bring into this picture the thoughts on theory of one of the great thinkers of all time, namely, Albert Einstein. Slide 5 presents Einstein's thoughts on theory:

"A theory is the more impressive: (1) the greater the simplicity of its premise is; (2) the more different kinds of things it relates; and (3) the more extended its area of applicability.

Keeping in mind Einstein's fundamental thoughts on theory, let us test the Hueper theory of arteriosclerosis. Dr. Wilhelm C. Hueper, after

Einstein's Thoughts On Theory

"A theory is the more impressive:

(a) the greater the simplicity of its premise is;

(b) the more different kinds of things it relates:

(c) the more extended its area of applicability."

Hueper's Anoxema Theory Of Arteriosclerosis

"Atherosclerosis results from a disturbance of the oxidative and lipoid metabolism of the body which permits the precipitation of Cholesterol."

SLIDE 5

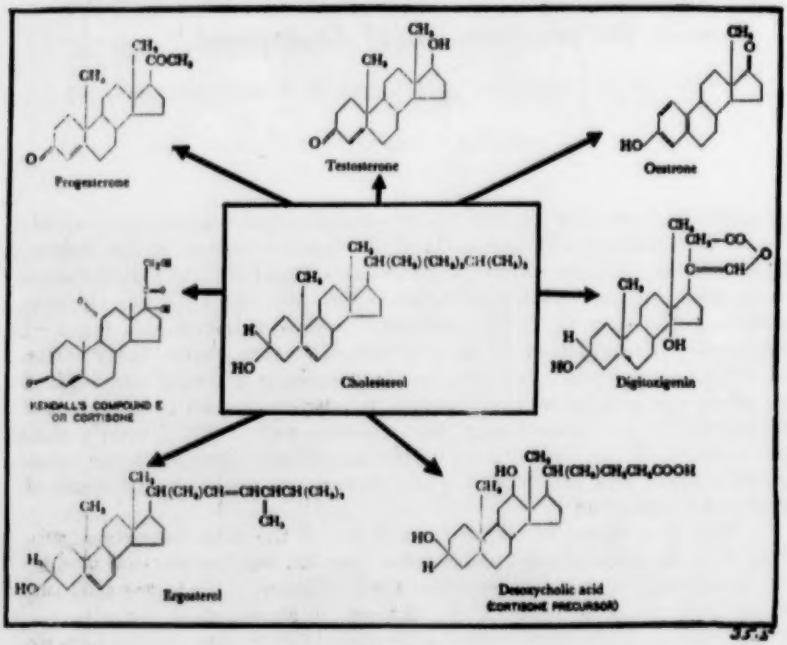
an exhaustive analysis of the varied clinical, pathological and experimental data dealing with hardening of the arteries arrived at the following conclusion. Simply stated: "Atherosclerosis results from a disturbance of the oxidative and lipoid metabolism of the body which permits the precipitation of cholesterol." This conforms to Einstein's first idea (1), i. e., the greater the simplicity of its premise. In other words, the *common fundamental action* through which the many etiologic factors of our civilized life affect the arterial wall is through an *interference with the oxygen and fat metabolism* and nutrition of the vascular wall. (Dr. Netter's slide No. 1 shows all these factors by simply and clearly illustrating the forming of atheroma in the intima. The plaques are primarily the result of cholesterol deposition.)

What is cholesterol? Cholesterol is one of the most important substances in the human body. It is not a true fat, but has physical properties resembling fat and is therefore called a "lipoid." It is probably one of the ancestral compounds, as it is present in almost all living cells.

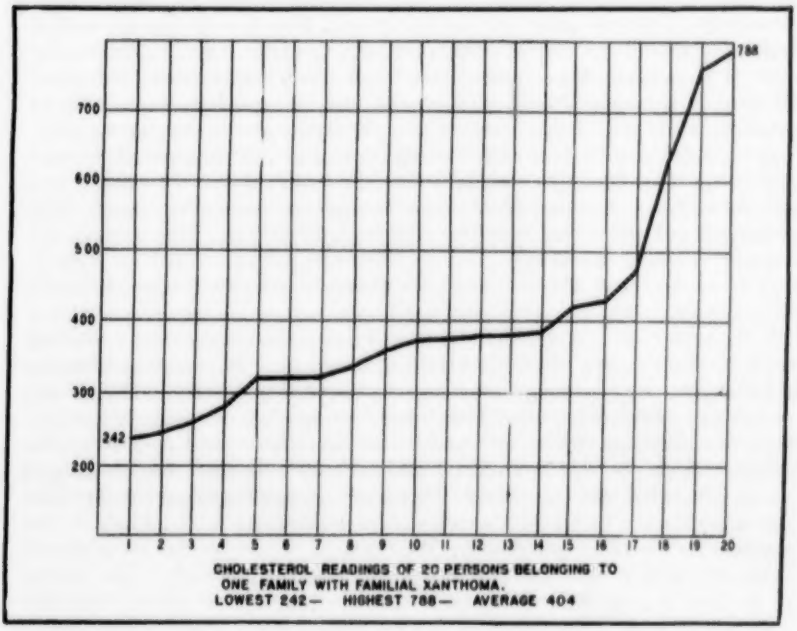
A review of the importance of cholesterol in human metabolism explains why I attribute so much to the Hueper theory: it conforms to the

second Einstein concept (2), i. e., the more different kinds of things it relates. Note the structural formula of cholesterol in the center. Note that despite its complex chemical structure, it is basically very similar to the other compounds on the slide. These 7 were taken from an infinite number which have as their base the cholesterol radical. The upper 3 are sex hormones which should be of particular interest to your research group. In the lower left is vitamin D, ergosterol; in the lower right is a bile acid-desoxycholic; to the left is Kendall's compound E or cortisone, the most recently publicized hormone of the adrenals, one of the probable 23 hormones of the adrenal glands. The fundamental importance of cholesterol in sterol chemistry should be obvious. It should also be obvious that a disturbance of the metabolism of cholesterol must create profound changes in the human body other than in the arteries, because of the importance of cholesterol in the makeup of the steroid hormones. It can be seen then, that a disturbance of cholesterol metabolism, which relates to so many hormones, can have an "area of applicability" (Einstein's third criterion) almost to infinity.

It is for these reasons that I make this statement: Hueper's anoxemia theory, when carried to full fruition, will create changes in the approach



SLIDE 6



SLIDE 7

to the whole of medical thought in the same manner that the Einstein theory integrated many concepts in physics.

Up to now we have reviewed atheromatosis in relation to the whole subject of arteriosclerosis; we have pointed out the etiologic factors and some mortality statistics to indicate the importance of the subject; we have emphasized the significance of the Hueper theory by illustrating the importance of cholesterol in abnormal and normal metabolism.

Now we finally come to the specific subject of today's discussion: "cholesterol atheromatosis, hereditary aspects." You are referred to the September 24, 1949 issue of the *J. A. M. A.*, "Genetics of Atherosclerosis" (Adlersberg, Parets and Boas of New York) which reviews the subject carefully, showing incontrovertible evidence that the manufacture of cholesterol is the result of hereditary factors and that atherosclerosis is even more frequently produced in people who synthesize cholesterol at a higher-than-average level. The disease is called "Familial Xanthomatosis." I shall only touch the high spots: (a) what we know of its hereditary character; (b) how we can use the findings in approaching the control of hardening of the arteries.

Therefore, I shall not go into the stigmata of the disease except to

say that it is characterized by hypercholesterolemia (a higher-than-average-level of cholesterol in the blood) and that it is associated with a high incidence of cholesterol atheromatosis, especially coronary artery disease. I have taken from their charts (Slide No. 7) cholesterol readings of 20 persons belonging to one family with familial xanthomatosis, only to show the variation of cholesterol levels. The slide shows the various readings from 242 mg. % lowest to 788 mg. % highest. The serum cholesterol average is 404. It can be seen how futile it is to deal with "average" cholesterol readings. The so-called normal cholesterol reading for certain areas of the general population is in the neighborhood of 210. This is really the average cholesterol reading. To consider 210 normal would be equivalent to saying that 404 is normal for these 20 individuals, an obviously wrong deduction.

Therefore, it is important to consider a person's cholesterol reading an individual matter, like his height and weight. A person reaches his adult height due to the play of various hereditary factors. This height remains constant. A person's cholesterol range, i. e., the person's ability to synthesize and utilize cholesterol, should remain as constant as the height. However, due to external and internal influences, the cholesterol varies somewhat like the weight. Of particular significance is the fact that the quantitative factor or the amount of cholesterol in the blood is not necessarily the most important. We know it is possible for some people with very high cholesterolemia to live to a relatively old age. The answer to this lies in a qualitative factor, i. e., in the proper *ratio* of the other factors which keep the cholesterol from precipitating. These other factors are, roughly, thyroxin and the oxytropic members of the B complex, thiamin chloride, riboflavin, niacin; the lipotropic factors—choline, inositol and pyridoxin; the phospholipids, albumins, and globulins in the plasma, etc.

As you can see, then, among the primary facts to be derived from this talk are: (1) that each person has his own individual cholesterol mechanism, inherited, as eye color or height; (2) that quantitatively, cholesterol itself is not necessarily dangerous, unless those factors normally holding cholesterol in suspension become deficient or disturbed, thus setting the stage for atheromatous deposits to create the organic change in the blood vessel.

EFFECT OF THERAPY ON A CASE OF FAMILIAL XANTHOMATOSIS WITH CORONARY DISEASE

	12-24-40	11-27-41	12-4-42	12-11-42	1-4-43	2-4-43	3-4-43	4-2-43	4-12-43	4-20-43	
Total Cholesterol	486	432	300	277	162	259	235	256	284	340	Mg. %
Ester Cholesterol	384	334	240	180	93	180	167	190	180	284	Mg. %

Therapeutic Agents

Oxytropic Factors	Lipotropic Factors
Ext. Thyroid	Choline Dihydrogen Citrate
Thiam. Chloride	Inositol
Riboflavin	Pyridoxine Hydrochloride
Niacinamide	
Ascorbic Acid	

SLIDE 8

Having given you a glimpse of this hereditary disease, familial xanthomatosis, I felt it might be interesting to show the effect of present-day treatment on such a patient. All the known oral therapeutic agents, which tend to prevent precipitation of cholesterol, are listed. The oxytropic factors are those which increase the oxidative power of the cell. This improved cellular metabolism increases the cellular use of cholesterol. The lipotropic factors of the B complex, by aiding in the transport and breakdown of the large globules of fat into smaller, more usable particles, help in the more rapid and effective utilization of cholesterol. The actual chemistry and physiology of the mechanism are not part of the present subject matter.

This patient responded spectacularly, as can be seen from the above readings. In general it has been found that between the first and third month of this treatment, a point is reached where the utilization of cholesterol outstrips the manufacturing ability of the individual. It is at this point that most of the patient's symptoms disappear, and that the reversal of the atherosclerotic process could theoretically take place, i. e., when the cholesterol level in the blood is so low that in the process of seeking the patient's normal cholesterol level, there would result the removal of cholesterol from its deposits in the blood vessels.

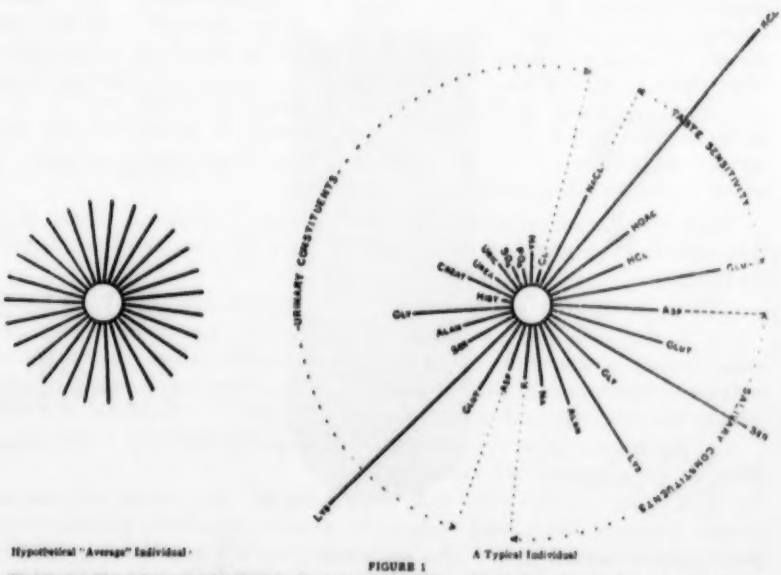


FIGURE 1

The following abbreviations are used in Figure 1: Creat = creatinine, Uric = uric acid, Hist = histidine, Gly = glycine, Alan = alanine, Ser = serine, Lys = lysine, Asp = aspartic acid, Glut = glutamic acid, Glu = glucose.

SLIDE 9

The remainder of this talk will deal with future prospects of arteriosclerosis control, as research in this problem becomes more and more specific.

To show that others are following the same type of approach, we wish to introduce the work of Dr. R. J. Williams. In a highly creative paper, "Individual Metabolic Patterns, Alcoholism, Genetotrophic Diseases," he and his collaborators came to the conclusion that "genetic patterns of individuals are conducive to the development of crucial deficiencies." This results in perverted appetites, such as alcoholism, and may also lead to organic and psychic diseases. Whereas Dr. Williams, as you can see from his diagram, uses as his measures creatinine, urea, uric acid, etc., which are products of metabolism, we go more fundamentally to the initiators of metabolic imbalance, the hormones and their satellites, the vitamins. We agree with the opinion that the future of hormonal therapy which is at present almost empirical, as far as hardening of the arteries is concerned, rests in the development of quantitative tests for hormones in the blood. For example, take the problem of hypercholesterolemia. Slide 10 is a schematic diagram of 100 cc. of blood after it is centrifuged. What are the factors which keep cholesterol from precipitating? As mentioned before, thyroid and some vitamins are involved. Do we know how much thyroid is necessary to keep cholesterol from precipitating? The same can be asked of choline and all the other vitamin factors. The same question can be asked of the phospholipid and the albumin fractions. At present no practical diagnostic test for thyroxin in the blood is available. Also, there is not set up a practical method of doing simultaneously on one sample of blood all these tests which would eventually tell us the story of cholesterol stability. Thus, we are forced at present to treat the patient empirically by overprotecting him with large doses of B factors which have been proved clinically to be harmless.

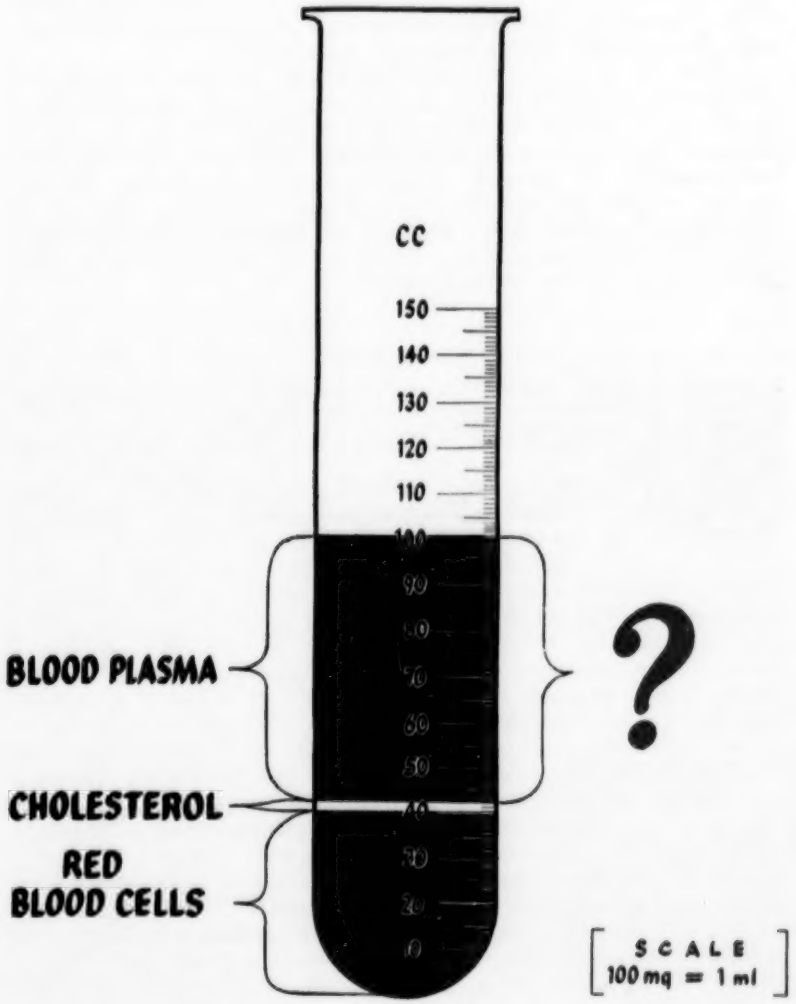
The elimination of arteriosclerosis from our civilization would produce effects so unbelievable as to be considered the dreams of an incurable optimist.

These happy effects in the next half-century will be:

1. A change in attitude toward people over the age of 60. Aging will have become a gracefully balanced process during which the intellect, instead of deteriorating, will continue to grow in power and stability—not torn by the excessive and unstable drives of youth.

2. Retirement at 90 or 100 instead of 60 and 65 will have a stabilizing effect on the economic and social world.

3. Respect for the older folk, something like the esteem of oriental peoples for their elders, will replace the present impatient, pitying, arrogant attitude toward them. The old themselves will lose their apologetic, hopeless attitude because they will have continued productivity. They will, in the process, have to lose the guilt feeling derived from their own youthful, arrogant attitude toward the old of their day.


CC
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
BLOOD PLASMA
CHOLESTEROL
RED
BLOOD CELLS
?
SCALE
100 mg = 1 ml

SLIDE 10

The eventual elimination of chronic metabolic diseases would necessitate the establishment of huge isotope-*prognostic* stations instead of present-day *diagnostic* clinics. There, with Geiger counters, rapid simultaneous studies of a person's metabolic pattern would be used to foretell and forestall organic disease, making diagnosis a rare necessity.

Now, let me say in summary that I hope the primary aim of this talk has been accomplished, that is, to show how a knowledge of hereditary factors can be used in the future control of atheromatosis. It is hoped, moreover, that you have noted the humility with which this subject has been presented. To those who believe in the senescence theory, this may seem an arrogant presentation because it has a disturbing effect on the status quo. To those willing to admit the tragic limitations of today's approach to the problem of arteriosclerosis, the humble desire to stimulate the search for truth will be apparent.

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A Systemically Effective Oral Dosage Form of Streptomycin

ROBERT D. BARNARD, M.D.

Recent reports[1] have tended to emphasize the superior mycobacteriostatic activity in vivo of streptomycin over aureomycin and other fermentatively produced antibiotics, so that the former would seem to remain the choice antibiotic, of its class, for the treatment of certain forms of human tuberculosis. This fact is pointed up by the additional recent finding that the development of "fastness" on the part of the organism may be of less practical, than theoretic importance. Many clinicians are inclining to the belief that protracted streptomycin therapy remains in order far beyond the expiration of the time interval when streptomycin resistance has become manifest in the organism against which it has been directed. On the erroneous assumption that streptomycin lost its therapeutic efficacy when the organism became "fast," many patients have been deprived of sustained courses of the antibiotic and the lives of many patients with meningeal or miliary forms of tuberculosis may have been needlessly sacrificed. Protracted streptomycin therapy, in face of resistance and in spite of it, has a rational basis in theory and is proving itself in practice.

The major disadvantages of streptomycin as compared with aureomycin were: it lacked the "virocidal" action of the latter and it was ineffective in producing therapeutic systemic tissue and plasma levels after oral administration. The first effect may be called into question by indications that the vaunted virocidal activity of aureomycin may merely have been the supportive and anticholinergic properties of the B_{12}-like substances (from the fermentation broth) with which the earlier preparations, at least, were replete. The absence of enteral absorption of streptomycin, on the other hand, constitutes a real disadvantage particularly when long-continued, ambulant or home treatment with streptomycin is indicated. Since it is the one antibiotic which is most frequently prescribed for specific indication (the others, it would seem, are now being used mostly on general principles), it appeared justifiable to attempt to develop an oral dosage form of streptomycin.

On the basis of the observation that certain streptomycin and dihydrostreptomycin aliphates have a detergent and "tweening" effect, in that they facilitate their own fine emulsification in aqueous menstruums[2], such a dosage form has evolved. Its use in practical therapy will be determined by the compromise that must necessarily be struck between the

apparent increased cost of an orally intended material (which in a very few instances approaches the disseminated tissue concentrations of parenterally administered materials) and its convenience or applicability. In the case of streptomycin therapy which is usually of long duration, the drug itself constitutes a considerable fraction of the cost to the patient. Offsetting the intrinsic cost of increased administered "unitage" which would be necessary for an oral preparation is the fact that such a preparation seldom requires the rigid purity control and sterility precaution and handling mandatory for parenterally intended materials. In this connection, a fortunate feature about all streptomycin preparations is their almost infinitely long stability in solution at ordinary temperature. Some of the preparations upon which this report is based have been stable, in that they showed no loss of unitage or ability to produce blood levels on oral administration, after standing for 18 months at room temperature.

In a previous communication, the ability of streptomycin aliphates in oil to form "deposits" or repositories of streptomycin after intramuscular injection into animals, was described. Such administration of the described materials is not contemplated for humans for it would appear to be unnecessary. Although the normal aliphates containing the higher fatty acids have very little "tweening" effect and would thus not be tissue irritants, it is believed that the promiscuous parenteral administration of antibiotics in general and of the oil suspensions of penicillin in particular has been responsible to a large degree for the atopies and pan-allergies that are now being encountered in medical practice. While sensitization by oral antibiotic preparations has occurred, it is probably of considerably less frequency and intensity. This was another consideration that led to an exploration of the possibilities of an oral streptomycin.

Experimental

The two preparations utilized for the study incorporated in this report are the streptomycin suboleate (a mixture of monoleates and dioleates to which the previously described oleocarbonate reverts on standing, with loss of CO_2) which has been administered only to dogs, and dihydrostreptomycin oleate emulsified in water through the agency of sorbitan monoleate polyoxyalkylene derivative (tween 80). The last component has been shown to be non-toxic for man when given in doses of 15 Gm. per day by mouth[3] and was added to the last preparation because of the negligible "tweening" effect of the normal oleate (vida supra). In the case of the suboleate, the use of extrinsic tween was unnecessary: it is itself homologous with tween 80 which is also a carbohydrate suboleate.*

Four dogs received streptomycin suboleate in water suspension by stomach tube in a single dose of 100,000 units (in terms of streptomycin base)/kilogram for each animal. Plasma streptomycin levels were deter-

*It appears that the addition of tween 80 will nevertheless enhance the absorption of the subaliphates of streptomycin, as indicated by preliminary experiments not incorporated in this report.

mined at the outset of the experiment (to correct for any intrinsic bacteriostatic activity of the plasma) and at the ends of the 4, 8, 12, 16 and 24-hour periods. The results are rendered graphically in Figure 1.

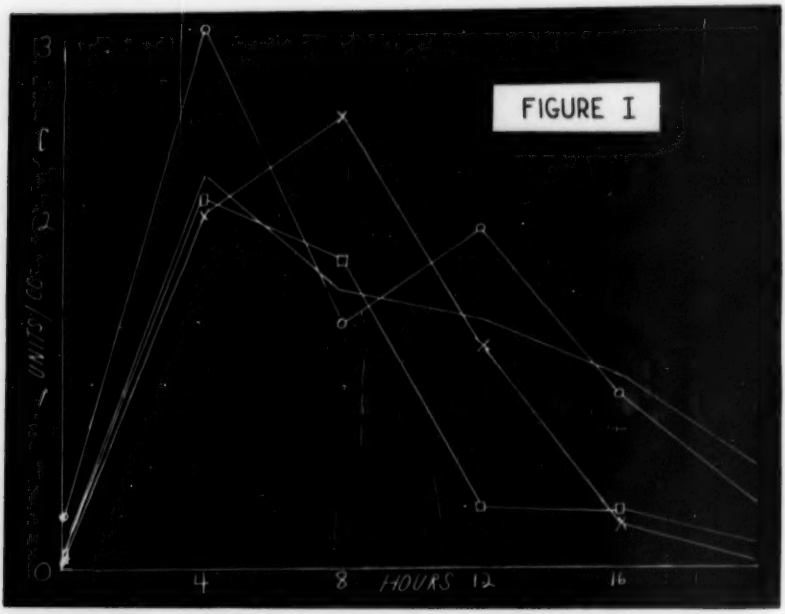

FIG. 1. Plasma streptomycin levels in dogs following the administration of 100,000 units of streptomycin suboleate kilogram.

Plasma levels are obviously established before 4 hours and a therapeutic level (arbitrarily established at 0.6 units/centimeters of plasma) are persistent at 16 hours. Detectible but immeasurable levels were found at 24 hours, justifying an interpolation for a 20-hour figure on the graph and on this basis, only one animal may have had a therapeutic level at this time. The average maximum effect of a single dose, by these data, is between 4 and 8 hours. It was predicted that a "climbing" level could be procured by a 6-hour dosage schedule but, because of technical difficulties, this was not attempted in animals. Instead, an improved dosage form for human administration was improvised. This consisted of a mixture of dihydrostreptomycin oleate in sesame oil dispersed in a sufficient amount of 4% aqueous tween 80 so that one-half ounce of final mixture represented 1½ million units (in terms of dihydrostreptomycin base). With the latter preparation in doses of one tablespoonful in milk, coffee or fruit juice, every 6 hours, such a "climbing" level was demonstrated by the second day in all of 6 patients. The levels, though not nearly approaching those to be

attained by parenteral administration, are well above the arbitrary therapeutic minimum at the end of 24 hours. Figure II represents the graph constructed from the daily blood levels of the patient who received the

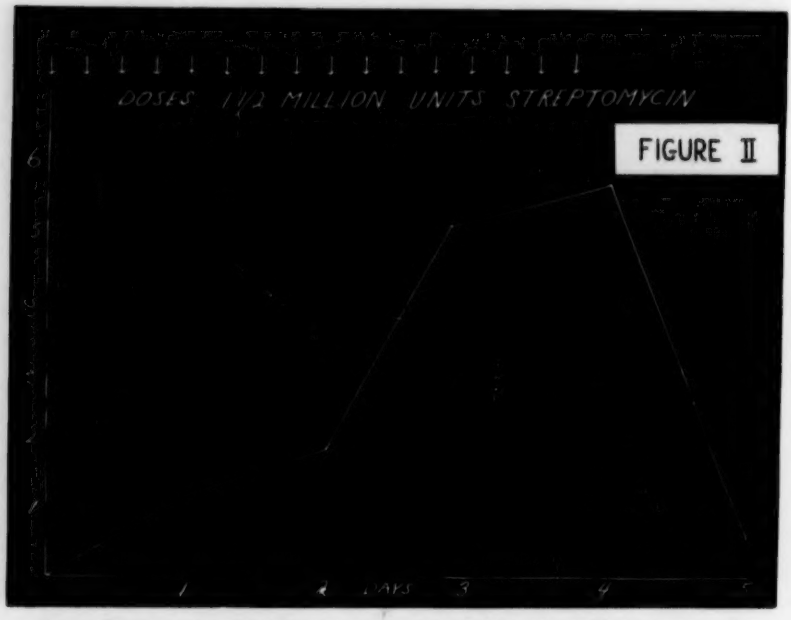

FIG. 2. Plasma streptomycin levels following repeated administration of dihydrostreptomycin oleate in sesame oil with tween 80, in a man weighing 73 Kg. The actual streptomycin concentrations were probably higher, some fraction being carried in the plasma in the form of the oleate which is not readily assayable. The climbing level is illustrated. The dosage (6 million units/day) is considered to be higher than desirable for a clinical product but lower dosage could presumably be used following tissue saturation (either by the parenteral or oral route). Figures not shown have indicated the possibility of maintaining a plasma streptomycin level of 5 units/cc., once established, by the administration of 2½ million units of the oral preparation daily.

preparation for 4 days. From the rise evinced on successive days, it is likely that the increment could be continued beyond the period occupied by this particular set of observations.

DISCUSSION

Aside from the practical therapeutic aspects of a systemically effective oral dosage form of streptomycin, its development points up certain features of the physiology of absorption that have only recently been clarified. The role of detergents, even those naturally occurring in the intestinal tract (the bile salts) was at one time restrictively assigned to the digestive

process. While the role of the lacteal villi in absorbing particulate matter sufficiently disperse has been known for decades, the significance of this extraportal absorption route, that would circumvent the liver in attaining entrance to the blood stream, is only now beginning to be appreciated. On this basis it is entirely possible that the failure of the ordinary water soluble streptomycin salts to appear in demonstrable concentrations in the plasma after oral administration (except in the 10% of individuals where it does so appear) may be due as much to hepatic inactivation as to intestinal impermeability. How far this case is true for streptomycin, can only be demonstrated by further study. In the case of another reputedly inabsorbable material, insulin, recent demonstrations of an inactivating agent within the liver[4] makes it appear likely that such inactivation plays a greater part in oral inefficacy than either tryptic digestion or the large size of the insulin molecule. That the natural route for insulin incretion is, in part, directly into the systemic circulation must be obvious to anyone who has considered the complete venous drainage of the pancreas. It is curious that those few, very moderate successes in obtaining oral insulin effect[5] have invariably been attained by admixture of the insulin with saponins, sodium lauryl sulfate, resorcinol derivatives or the lipoid material from ascaris—all were detergents added in the hope of inhibiting tryptic digestion but quite probably operating (in this connection) as emulsifiers which reduced particle size to that point where lacteal villous absorption with portal bypassing was feasible. This concept of the possibility of oral systemic introduction of previously considered "inabsorbable" medicinals may develop into an important benefit to practical therapeutics accruing from introduction of the "tweening" agents.

That some of the streptomycin carried by the plasma, after the oral administration of the described derivatives, is in the form of the oleate is suggested by an observation made during the plate assay for plasma levels. Frequently, around the complete clarification zone whose diameter was an index of the streptomycin content extant, there would be a much wider concentric zone of only partial clearing. The latter could be attributed to a relatively insoluble form of the antibiotic such as the oleate. The observation is of double significance. It indicates that the actual total streptomycin content of the plasma may have been considerably higher than that expressed by the complete zone of clarification in these experiments. It also means, if correctly interpreted, that the streptomycin molecule with its almost specific demonstrability on the basis of organism assay (such as is represented by the streptomycin requiring organisms) could be used as a "tracer" molecule for the "tagging" of aliphatic acids to follow their metabolic course. This technic now in vogue with various isotopes might turn into another application of antibiotics.

Summary

An oral dosage form of streptomycin which yields systemic plasma levels is described. It is based on circumventing the portal-hepatic absorption route through the use of a fat soluble or dispersible streptomycin aliphate which is emulsified with a "tweening" agent. The application of this principle for obtaining systemic effect with other medications is discussed, as well as the possible use of antibiotic moieties as metabolic "tracers."

SMITH BUILDING, FAR ROCKAWAY, L. I., NEW YORK CITY.

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Hyperchloremic Acidosis and Potassium Deficiency Following Total Cystectomy and Bilateral Ureterosigmoidostomy*

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DONALD W. DREW, M.D., AND EDWARD J. WISS, M.D.,
Fellows in Internal Medicine

Successful bilateral ureterosigmoidostomy is achieved with increasing frequency by control of its heretofore serious complications. Indications for this procedure are found chiefly in certain congenital anomalies of the lower urinary tract and in malignant lesions of the bladder or prostate causing obstruction. This report describes an unusual, severe complication of ureterosigmoidostomy with its care and prophylaxis.

REPORT OF CASE

A 54-year-old man entered the hospital in July 1949 complaining of urinary frequency, nocturia and dysuria for the previous four months, and of bloody urine for the previous six weeks. Cystoscopic examination revealed an extensive carcinoma involving the right side of the bladder and encroaching upon the right ureteral orifice. An intravenous pyelogram showed a normal upper urinary tract with prompt excretion of the dye in five minutes. Urinalyses revealed the specific gravity to range from 1.008 to 1.010 with albuminuria from 0.05 Gm.% to 1.23 Gm.% concentration. Microscopic study of the sediment showed red blood cells from few to packed per high power field, but no casts or white blood cells were noted. The nonprotein nitrogen was 35 mg. per 100 cc., hemoglobin 17.0 Gm., white blood cells 10,600 per cu. mm. and the differential count was normal (Table I, first admission). Cystectomy and bilateral ureterosigmoidostomy were deemed mandatory and were done without incident.

The nonprotein nitrogen rose to 82 mg. per 100 cc. on the sixth postoperative day, but fell to 45 mg. per 100 cc. at the time of discharge on the twentieth. His recovery was otherwise uncomplicated except for transient partial atelectasis of the upper lobe of the right lung.

The patient was admitted five weeks later because of intractable hiccuping associated with mild uremia and moderate acidosis (Tables 1, 2 and 3, second admission.) He was treated with intravenous infusions of 5% dextrose in water, 500 cc. of whole blood, luminal, intravenous calcium gluconate, carbon dioxide inhalations, codeine and atropine. The hic-

*Reprinted from *The Lahey Clinic Bulletin*, April 1950 (Vol. 6, No. 8).

cuping stopped abruptly on the seventh day of treatment, and he was discharged in apparently good condition on the ninth hospital day, although the carbon dioxide combining power was still low at 12 mEq. (28 volumes %).

He was readmitted three weeks later because of recurrent hiccuping, and lapsed into a stuporous state. Blood chemistry determinations revealed severe acidosis with a carbon dioxide combining power of 9 mEq. (21 volumes%; Tables 1, 2 and 3, third admission); the nonprotein nitrogen levels varied from 49 to 75 mg. per 100 cc. The rectally voided urine was clear and contained no significant sedimentary elements. On the fifth hospital day, the serum potassium was 12.8 mg. per 100 cc.; the blood creatinine concentration was normal. Treatment was carried out with barbiturate sedation, carbon dioxide inhalations, whole blood transfusions and parenteral fluids in large quantities, including ⅙ molar lactate.

Clinically the patient was improved after the first day of high fluid intake which reached a maximum of 5½ liters with a subsequent peak urinary output of 5 liters per twenty-four hour period. He was discharged on the thirteenth hospital day in excellent condition and instructed to empty the bowel frequently and force fluids to at least 3 liters per day.

He remained well for two weeks when he noted anorexia, then suddenly chills, weakness and dyspnea developed, and he was brought to the hospital semiconscious. Studies of blood chemistry showed a moderate uremia and severe acidosis with a carbon dioxide combining power of 6 mEq. (14 volumes %). Serum potassium was 9.7 mg. per 100 cc. and the electrocardiogram showed a pattern consistent with hypokalemia (Fig. 1). Pertinent blood chemistry studies and parenterally administered fluids are summarized in Figure 2. Potassium was given orally and rectal lavage was carried out with 5% sodium bicarbonate solution. In forty-eight hours, the patient was clinically normal; the carbon dioxide combining power was 8 mEq. (19 volumes %) on the second hospital day and 27 mEq. (62 volumes %) on the fourth hospital day. The nonprotein nitrogen reached a maximum level of 90 mg. per 100 cc. No hypokalemic effect could be discerned in an electrocardiogram repeated on the fourth hospital day (Fig. 1). On intravenous pyelography the calices or ureters were not visualized, but a few puddles of dye did appear in the bowel, a finding in contrast to urograms taken before operation five months previously. He was discharged on the eighth hospital day on the following regimen: sodium bicarbonate 1 Gm. orally four times a day, low salt diet, 3 liters of fluid by mouth daily and instructions to sleep in the semi-Fowler's position, preferably on the left side. He was also told to arise to evacuate the bowel content at least three times during the night. By following this regimen he had no further trouble and has been gainfully employed for the last five months. Current check reveals his clinical condition to be excellent and his laboratory studies normal except for a moderately elevated nonprotein nitrogen level and slightly lowered carbon dioxide combining power (Tables 1, 2 and 3, Follow-up).

Discussion

Acidosis from mild to moderate degree has been noted in 62% of a series of cases by workers at the Mayo Clinic[2] after ureterosigmoidostomy. They suggest that reabsorption of urine from the large bowel may account for this complication. Prior to operation there were no clinical symptoms to suggest renal insufficiency or acidosis. Laboratory studies had shown an essentially negative urine except for albuminuria and a relatively low fixed specific gravity (1.008 to 1.010). The intravenous pyelogram revealed prompt excretion of dye with normal kidney outlines and calices and the preoperative nonprotein nitrogen was normal. These findings suggest a borderline but compensated kidney function in an individual with nephrosclerosis. Presumably the results of the operative procedure tipped

TABLE 1

Laboratory Data—Blood Chemistry Findings

Admission	*Nonprotein nitrogen, mg. per 100 cc. (hospital day indicated)*	*Carbon dioxide, mEq. (hospital day indicated)*	*Blood Counts*		
			Hemoglobin, Gm.	*Leukocytes*	*Differential*
1 7-29-49	35 (1st) 82 (6th) 45 (29th)		17 0	10,600	Normal
2 10 3 49	52 (1st)	12 (1st) 12 (8th)	13 0	29,300	Normal
3 11-3-49	49 (1st) 75 (3rd) 42 (13th)	9 (1st)	10 6	36,100	Normal
4 11-30-49	80 (1st) 90 (2nd) 66 (4th) 43 (6th)	6 (1st) 8 (2nd) 27 (4th) 28 (6th)	11 0	17,400	Normal
Follow-up Jan. 1950	55	15			
Follow-up Feb. 1950	60	18			

TABLE 2

Laboratory Data—Urinalyses

Admission	*Specific gravity*	*Albumin, Gm.*	*Erythrocytes per h.p.f.*	*Leukocytes per h.p.f.*	*Sugar*	*Ketone bodies*
1	1 008- 1 010	0 05- 1 23	few—packed	0	0	0
			Voided Rectally			
2	1 008	0 07	0	packed	0	0
3	1 008 1 015	0 05	0	few	0	0

TABLE 3

LABORATORY DATA
MISCELLANEOUS BLOOD CHEMISTRY FINDINGS

Admission		*Values (hospital day indicated)*
2 10-3-49	Chlorides	111 mEq.
3 11-3-49	Sugar	105 mg. per 100 cc. (1st)
	Creatinine	2.5 mg. per 100 cc. (1st)
		1.6 mg. per 100 cc. (13th)
	Chlorides	104 mEq. (4th)
	Calcium	9.2 mg. per 100 cc.
	Phosphorus	3.9 mg. per 100 cc.
	Potassium	12.8 mg. per 100 cc. (5th)
	Alkaline phosphatase	3.4 B.U.
	Acid phosphatase	0.3 B.U.
4 11-30-49	Chlorides	126 mEq. (1st)
	Potassium	9.7 mg. per 100 cc. (2nd)
		18.7 mg. per 100 cc. (6th)
	Serum protein	7.3 Gm. per 100 cc.
Follow-up Jan. 1950	Chlorides	121 mEq.
	Sodium	141 mEq.
Follow-up Feb. 1950	Chlorides	92 mEq
	Sodium	147 mEq.

the balance leading to uremia and acidosis. The degree of acidosis, however, seemed to be far out of proportion to the degree of uremia. Surely many cases of moderate uremia are seen with little or no clinical disturbance in the acid-base equilibrium. Severe acidosis owing to failure from nephrosclerosis sufficient to produce a semicomatose state seldom responds so promptly to medical management.

To trace the causes of this delayed decompensation of kidney function, the usual complications of the operative procedure were sought. Incomplete ureteral obstruction at the anastomotic site with hydronephrosis or an ascending urinary tract infection with pyelitis was first considered. The marked, prompt diuretic effect following parenteral fluid therapy seemed to rule out significant obstruction and although satisfactory urograms could not be obtained on the third postoperative hospital admission, the kidney outlines appeared within normal range. Pyelonephritis did not appear to be an important factor because of the clear urine and lack of fever, chills and local tenderness. Thus other factors were sought; a metabolic error appeared plausible.

The conservation of sodium and chloride ions is a well recognized and important resorptive function of the colon, the stools normally containing little of these elements.[2] The kidney function conversely is to excrete or retain sodium and chloride in accordance with the body's needs.

Ureteral transplant to the colon obviously may bring important quantities of sodium and chloride, destined for excretion, to an organ which

accepts them. The resultant possibilities for a vicious circle ending in a chloride acidosis is apparent.

One or a combination of three following mechanisms is thus available:

1. Selective absorption of chloride ion.
2. Absorption of both sodium and chloride ions as sodium chloride.
3. Absorption of both ammonium and chloride ions.

Absorption of chloride might lead directly to hyperchloremia, the electrical neutrality of the serum being achieved by decrease of bicarbonate ion concentration through the respiratory mechanism.

Sodium chloride absorbed as such also results in preponderance of chloride ion in the serum because of the difference in milliequivalent relationship between molecular sodium chloride and the ionic concentration of these elements in serum and extracellular fluid. Molecular sodium chloride has the relationship of one milliequivalent of sodium to one milliequivalent of chloride (ratio 1 to 1). In the body sodium and chloride bear the relationship of 1 to 0.7, leaving an excess of chloride ion amounting to 0.3 milliequivalents, permitting a potential chloride acidosis.

In the case of ammonium chloride, the ammonium ion may be changed to urea, leaving the chloride ion to displace the normal bicarbonate ion component. The urea, of course, could contribute to the azotemia.

Important corroborative evidence that absorption of urine causes hyperchloremic acidosis is found in a recent case following colostomy and ureteral transplant wherein urinary pooling was permitted.[4] Vigorous medical management was fruitless in correcting this acidosis until intestinal continuity was restored and the urinary stasis was abolished. Satisfactory improvement promptly followed.

The usual disappearance of this tendency to acidosis about six months after ureterosigmoidostomy[3] suggests to us that the colon may alter its function to permit adjustment to the extra chloride that is offered under these circumstances.

The following is a comparison of serum electrolyte patterns in the acidosis of renal insufficiency (retention) and in this case of ureterosigmoidostomy (reabsorption).

	Acidosis of Renal Insufficiency (Retention)	*Acidosis of Ureterosigmoidostomy (Reabsorption)*
1. Serum Concentration chloride ion	Often decreased	Increased
2. Serum concentration phosphate ion	Usually increased	Normal
3. Serum concentration sodium ion	Usually decreased	Normal
4. Serum concentration potassium ion	Normal or increased	Decreased

We presume the hypokalemia was secondary to acidosis[1] and catabolism of starvation (food restriction because of the gastrointestinal upset, anorexia and hiccuping). In addition, there was probably considerable washing out of the ion by diuresis induced by forced fluids.

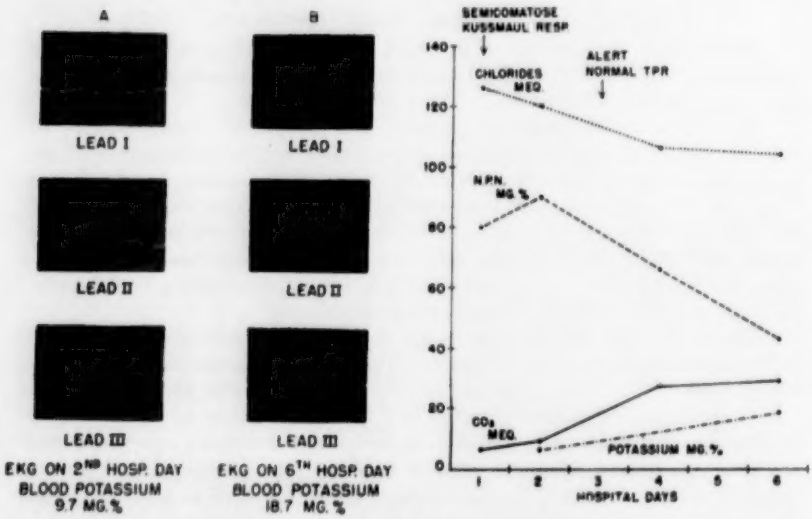

FIG. 1. Lead I first electrocardiogram (A), Q-T interval is 0.44 second (exceeds one-half R-R interval). Low voltage of T waves with ST sagging Leads I and II. Note normal relationship in second electrocardiogram (B).

FIG. 2. Therapy summary by hospital day.

First, 1500 cc. $\frac{1}{6}$ molar sodium lactate by hypodermoclysis, 1000 cc. 5% glucose in water by hypodermoclysis

Second, 1500 cc. $\frac{1}{6}$ molar sodium lactate by hypodermoclysis, 3000 cc. 5% glucose in water by hypodermoclysis, rectal lavage with 5% sodium bicarbonate solution every three hours while awake (2500 cc. per twenty-four hour period)

Third, 1500 cc. $\frac{1}{6}$ molar sodium lactate by hypodermoclysis, 1500 cc. 5% glucose in water by hypodermoclysis, potassium chloride 1.0 Gm. three times daily by mouth

Fourth, 500 cc. $\frac{1}{6}$ molar sodium lactate by hypodermoclysis, 1000 cc. 5% glucose in water by hypodermoclysis, potassium chloride 1.0 Gm. three times daily by mouth

Fifth, 1000 cc. 5% glucose in water by hypodermoclysis, potassium chloride 1.0 Gm. three times daily by mouth

Sixth, potassium chloride 1.0 Gm. three times daily by mouth

Thus, there is acidosis due either to kidney failure or to a metabolic defect resulting from reabsorption of urine. We present clinical and electrolytic pattern evidence that the acidosis is caused mainly by reabsorption of urine with resultant hyperchloremia. The process possibly is facilitated by reduced tubular function.

Summary

A case is presented in which hiccuping was a prominent feature in severe recurrent, debilitating acidosis following ureterosigmoidostomy.

The presumed basis for this acidosis is discussed, emphasizing the importance of the colon's selective reabsorptive power acting on a fluid destined normally to be delivered outside the body.

Treatment and prophylaxis are outlined, stressing the need for additional base, limitation of chloride and reduction of contact of the urine with the colon by its dilution and frequent evacuation.

An incidental finding of hypokalemia with consistent electrocardiographic change is recorded.

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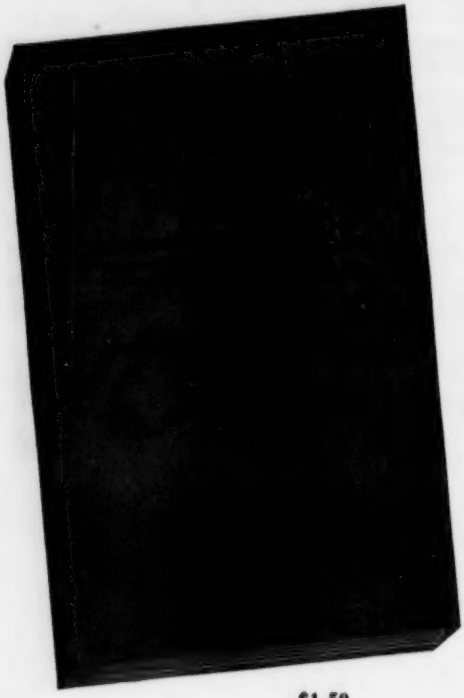

The title, "Marihuana in Latin America, The Threat it Constitutes," does not do justice to the wide scope of this monograph. While Dr. Wolff has placed particular emphasis on Latin American aspects, his discussion is of general application and interest. He has made a painstaking review of information on the abuse of cannabis. It is a much needed compilation of current knowledge in one volume. The author has done his usual erudite, well documented job. The style is interesting, and the book is recommended to readers desiring a comprehensive and accurate view of this field. The bibliography is extensive.

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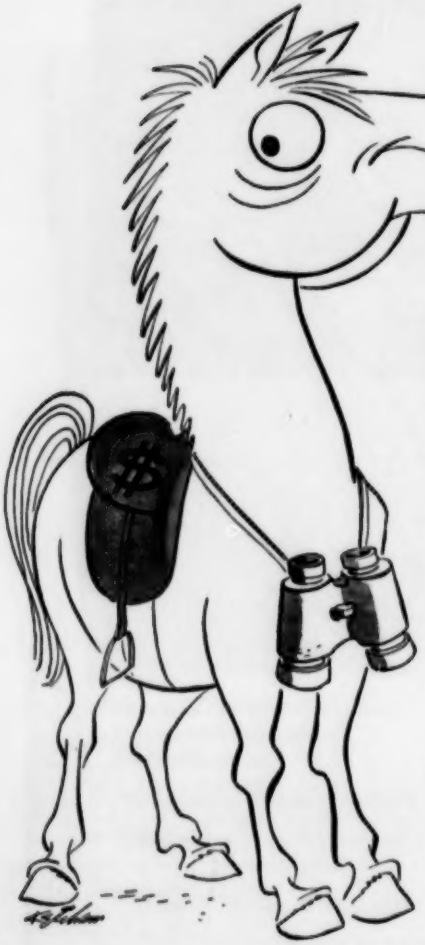
"There's no such animal," he cried!



MY FRIEND and I were picking the ponies one day when I started telling him about *a sure thing* I heard about.

"You say it pays four bucks for every three?" he asked.

"Yep," I replied.

"And can't lose? It *automatically* wins? Must be illegal!"

"Not a bit," I replied. "In fact, the government very much approves . . ."

"Our government approves of a horse who can't lose . . ."

"Who said anything about a horse?" I asked.

"So what else could it be but a horse . . .?"

"It not only could be—but is—U. S. Savings Bonds," was my prompt reply. "The surest thing running on any track today.

"For every three dollars you invest in U. S. Savings Bonds you get four dollars back after only ten years. And if you're a member of the Payroll Savings Plan—which means you buy bonds *automatically* from your paycheck—that can amount to an awful lot of money when you're not looking. Hey, what are you doing?"

"Tearing up my racing form! The horse I'm betting on from now on is U. S. Savings Bonds."

Automatic saving is <u>sure</u> saving—U.S. Savings Bonds

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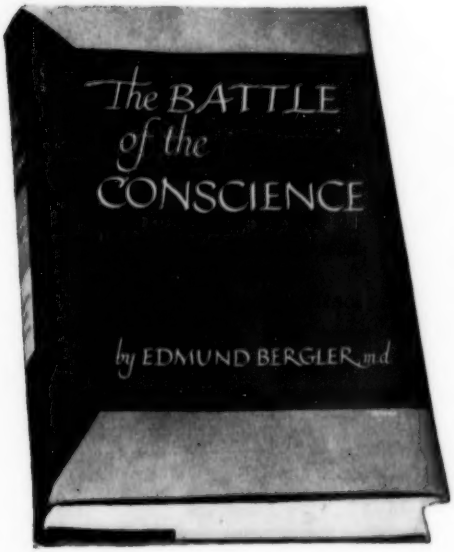
The Battle of the Conscience

By
EDMUND BERGLER, M.D.



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